NATURE OF THE CONTRACTION OF MUSCLE*

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THERMODYNAMICS deals with the relations between different forms of energy and entropy in equilibrium reactions. If applied to muscle it could give us a deeper insight into the nature of contraction : but before it can be applied, one of the most basic questions of biology has to be answered : Are complex biological phenomena, such as contraction in muscle, made up of equilibrium reactions ? Only if these effects are made up of such equilibrium reactions can thermodynamics be applied. This question, however, cannot be answered without applying thermodynamics.

There is one way of breaking this vicious circle : by observing what muscle does under conditions in which thermodynamic regularities can reveal themselves (that is, varying one of the main thermodynamic parameters, temperature or pressure), applying thermodynamics to the results and then seeing whether it makes sense.

There are two changes we can conveniently measure in contraction : shortening (at constant tension), and tension (at constant length). A third important characteristic of muscular activity is the work-integral, the maximal working capacity. Its curve is practically identical with that of the tension. In order to transform the curve of tension into a curve of maximal working capacity, on first approximation we only have to change the units of gram-weight of tension on the ordinate into the corresponding calories.

These changes were measured at varied temperatures in a number of widely different muscle preparations, such as the frog sartorius and rat diaphragm excited electrically, the rabbit psoas excited by freezing and thawing or brought to contraction in the washed condition by adenosinetriphosphate. In spite of the great differences in the nature of these materials, all the curves of shortening were found to be very similar to one another, as were the curves of

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tension or work. The curves of shortening, however, were found to be very different from those of work or tension.

Starting from low values, on raising the temperature the curve of shortening rises, reaches a flat maximum, and declines at higher temperatures after forming a symmetrical wide arch. The curve of tension also rises first and declines later, its maximum being at the same point as that of the shortening ; but this curve of tension is composed of two straight lines with a smoothed-out transition.

Changes in tension show all the signs of thermodynamic reversibility ; when varying the temperature the tension follows in a regular fashion reversibly. Shortening shows limited signs of reversibility, being a function of temperature.

Working on the most probable assumptions, namely, that macroscopic shortening is the integral of the shortening of small units, 'autones', reacting in a first-order all-or-none equilibrium reaction, we can derive from the curve of shortening the equilibrium constant K of the hypothetical underlying equilibrium reaction for the different temperatures. Then, applying the van't Hoff isochore, $\Delta F = -RT\ln K$, from the K's we can calculate ΔF and compare it with our experimental curve of maximal working capacity. If allowance is made for the shortcomings and uncertainties of the technique, the calculated and the experimental curves are found to be in close accord, suggesting that contraction *is* an equilibrium reaction to which thermodynamics *are* applicable.

If log K is plotted against $1/T$, two straight lines are obtained, one corresponding to the ascending and one to the descending slope of the curve of shortening. This suggests that contraction is the result of two equilibrium reactions coupled in a peculiar fashion. At any temperature contraction is governed by whichever of the two has the lower K and is the 'bottle neck'. Thus, at a lower temperature the curves reveal the constant K of one of the two reactions, let us say R_1, while at higher temperatures the constant K_2 of the other reaction, R_2, is revealed. The tensions at lower temperatures correspond to the free-energy change of R_1, while the tensions at higher temperatures indicate the ΔF of R_2. Further thermodynamic analysis shows that the slopes of these curves are entropy-slopes and indicate great changes in entropy. There is also a considerable endothermic heat change, somewhat overcompensated by the simultaneous exothermic changes. The thermometer, in this case, could only indicate the small positive overall result. Similarly, the actual work produced by the muscle is merely the relatively small overall result of much greater changes in internal and

thermokinetic energy compensating one another to a great extent.

The concept of contraction given by thermodynamics tallies with the chemical experience, which shows the contractile matter to be built of two proteins, actin and myosin, coupled in a peculiar fashion. It also agrees with electron microscopic observation, which suggests that the autone of myosin is that segment of its molecule which reacts with an actin 'ovoid'. Evaluation of the curves indicates that the 'autones' contain a quantity of myosin corresponding to a molecular weight of 70,000.